UNITED STATES PATENT AND TRADEMARK OFFICE

C1C

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/654,163	09/03/2003	Timothy J. Guzi	OC01620K	4318

24265 7590 06/20/2005

SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530

EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/654,163	GUZI ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/22/04&12/15/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on 9/3/03. There are thirty-seven claims pending and thirty-seven under consideration. Claims 1-27 and 37 are compound claims. Claims 35 and 36 are composition claims. Claims 28-34 are method of using claims. This is the first action on the merits. The application concerns some N-sulfamido and N-ureido-pyrazolo[1,5-a]pyrimidin-7-amine compounds, compositions, and uses thereof.

Title

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: replacement of the word "Novel" by the phrase "N-Sulfamido and N-Ureido ".

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 28-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the definitions of the variables R^2, R^3, R^6, R^7, and R^{10}, in claim 1, the phrases "heteroarylalkyl" and "heterocycloalkyl" are indefinite. Neither phrase is defined in the specification and while the

individual parts of each compound word, "hetero", "aryl", "alkyl", "cyclo" do have meaning, the combinations are ambiguous. For example, both "heteroaryl" and "arylalky" have separate and distinct meanings but the word "heteroarylalkyl" does not and is indefinite. There is no such thing. Is it an alkyl substituted by a heteroaryl, e.g. pyridyl-methyl? An arylalkyl interrupted by a heteroatom, such as C_6H_5-CH_2-O-CH_2? An arylalkyl substituted by a heteroatom, e.g. 4-chlorobenzyl? Whatever choice is selected must be supported by the specification.

The word "heterocyclylalkyl" is also indefinite. There is no such thing. Is it an alkyl substituted by a heterocyclyl, e.g. piperidinyl-methyl? A cyclylalkyl interrupted by a heteroatom, such as piperidinyl? A cyclylalkyl substituted by a heteroatom, e.g. chlorocyclohexyl? Whatever choice is selected must be supported by the specification.

4. Claims 28-30 and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "a patient in need of" "inhibiting one or more cyclin dependant kinases". It is unclear what diseases and treatments applicant is intending to encompass. Determining whether a given disease responds or does not respond to such a receptor antagonist and thus,

covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite. The passage spanning line 15, page 19 to line 17, page 20 lists an impressive sum of such conditions. However, it uses open language. Is this the entire scope of the therapeutic claims or are there other diseases?

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative

skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim 1 as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

The Examiner suggests removing the phrase "or solvate" from the claims.

6. Claims 28-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating any human disease. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with claims 28-34 or to use claims 35 and 36. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. The factors to be considered in making an enablement rejection have been summarized above. The four main issues are the lack of any correlation between clinical efficacy for disease treatment and Applicants' *in vitro* assay, the lack of any biological data, the state of the prior art, and the breadth of the claims.

There is an *in vitro* assay, drawn to inhibition of cyclin A dependant kinase 2 enzyme (CDK2), described in the passage spanning line 19, page 64 through line 20, page 65 with no data. Applicants do not state and it is not recognized in the therapeutic arts this assay is correlated to clinical efficacy for the treatment of any disease diseases. The state of the clinical arts in CDK2 related diseases is provided by Fischer (Expert Opinion on Investigational Drugs, June 2003). Fischer (Expert Opinion on Investigational Drugs, June 2003) in section 7, psanning pages 962-964 states that in 2003, a year after Applicants effective filing date, the CDK2 inhibitor

flavopiridol had failed to show anti-tumor efficacy, the CDK2 inhibitor 7-hydroxystaurosporine had failed to show adequate PK propertities, and the third CDK2 inhibitor roscovitine had not been tested in efficacy trials. The state of the clinical arts in CDK2 related diseases is provided by Fischer (Expert Opinion on Investigational Drugs, June 2003). Fischer (Expert Opinion on Investigational Drugs, April 2005) in section 6, psanning pages 463-466 states that in 2005, three years year after Applicants effective filing date, the CDK2 inhibitor roscovitine stll had not been tested in efficacy trials, the CDK2 inhibitor flavopiridol had failed to show anti-tumor efficacy against renal cancer, the CDK2 inhibitor UCN-1 was about to be studies in ovarian cancer, and BMS-387032 had only been studies in a phase I trial. In section 10, page 469, he concludes "recent reports have questioined the validity of CDK2 as a good target for ... cancer".

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the unknown of diseases embraced by the term "a patient in need of" "inhibiting one or more cyclin dependant kinases". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to

make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Conclusion

7. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

8. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas McKenzie, Ph.D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If

attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.

Thomas C. McKenzie, Ph.D.
Primary Examiner
Art Unit 1624
(571) 272-0670

TCMcK/me